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New USP Dissolution Performance Verification Standard: What, Where, and When

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INTRODUCTION

On April 6, 2023, the United States Pharmacopeia (USP) presented a webinar entitled "New USP Dissolution Performance Verification Standard: What, Where, and When." The webinar was sponsored by the American Association of Pharmaceutical Scientists (AAPS) and AAPS In Vitro Release and Dissolution Testing (IVRDT) Community and was led by Mark Liddell (USP). The webinar aimed to provide an overview of the introduction of the new USP Dissolution Performance Verification Standard – Prednisone RS (DPVS – Prednisone) for use in performance verification tests (PVT), highlight associated revisions of the *USP* General Chapter (GC) <711> Dissolution, and reviews some frequently asked questions (*1*). This article summarizes the webinar content, including responses to frequently asked questions and points for consideration.

WHY A NEW PVT REFERENCE STANDARD?

The design and introduction of new refence standard material was motivated by discussion and feedback received from various USP stakeholders collected over many years while the previous formulation of the 10 mg USP Prednisone Tablet RS was available to the market. The reformulation and redesign of the new tablet is part of the USP's commitment to continuous improvement of its products and services.

WHAT IS THE NEW USP DISSOLUTION PERFORMANCE VERIFICATION STANDARD (DPVS)?

A target product profile for the new DPVS – Prednisone tablet was developed based on challenges with the previous USP Prednisone Tablet RS formulation. The following four targets were used to improve on the existing formulation: 1) the formulation should be sensitive to changes in the setup and operational parameters of typical USP apparatus 1 and 2 dissolution tests (e.g., vessel centering, rotation speed, paddle/basket height, vessel geometry, basket quality, etc.); 2) the formulation should not be over-sensitive to dissolved gases in the media; 3) decrease intra-run variability for apparatus 1 and 2 dissolution experiments; and 4) the formulation should be physically and chemically stable over the shelf-life of the product.

The starting point for the redesign of the new formulation was rooted in basic understanding of the hydrodynamics in apparatus 1 and 2, which led to a redesign of the shape and size of the PVT tablet. It is commonly understood that directly beneath the paddle there exists a region of low fluid velocity sometimes referred to as a "dead zone." It was thought that increasing the mass and size and changing the shape of the existing tablet would promote more consistent placement of the dosage form in the paddle apparatus and may also benefit the performance of the basket apparatus. Feedback from users indicated that the previous tablet would sometimes float to the top of the rotating basket when the basket was lowered into the dissolution media. In apparatus 2 experiments, the positioning of the tablet at the bottom center of the vessel would vary based how the tablet was introduced to the vessel at the start of the dissolution experiment. The previous tablet was a typical round, bi-convex tablet having a mass of 222 mg (total weight with 10 mg of prednisone). The new tablet shape is a modified sphere with a total weight of 350 mg (with 10 mg of prednisone), as shown in Figure 1A. Changing the mass and shape of the tablet led to more consistent placement of the tablet in both the basket and paddle apparatus.

In addition to changes in the formulation, a new packaging configuration has been used to protect the individual blister cards containing DPVS – Prednisone tablets from moisture (Fig. 1B). An aluminum sachet is used to protect each individual blister card, which contains six tablets

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per card. Stability tests were conducted under accelerated (40 °C, 75% relative humidity [RH]) and long-term (25 °C, 60% RH) conditions, and the blister cards stored in aluminum sachets were stable throughout the period of testing. Throughout the stability studies, the tablets were sensitive to changes in setup and operational parameters that were evaluated as part of the product development.

A B

*Figure 1. Photograph of the new United States Pharmacopeia dissolution performance verification standard - Prednisone RS tablets (DPVS - Prednisone) (**A**) and push-through blister packaging configuration (**B**).*

At each step of re-designing the formulation, whether selecting the formulation components or compression and manufacturing parameters for the new formulation, a set of three types of dissolution experiments were conducted to evaluate the sensitivity of the potential product candidates to different dissolution conditions. The first set of experiments were referred to as baseline experiments. In these experiments, the dissolution apparatus was configured to minimize any deviation in the standard setup/operational parameters (vessel centering, basket/paddle height, rotation speed, degassed media, etc.). In the second set of experiments, non-degassed media was used with the same dissolution system as the baseline experiments. The third set of experiments was referred to as a 'perturbed' system – degassed media was used with specific setup and operational parameters adjusted to the edge of specification limits allowed according to GC <711> and the USP Dissolution Toolkit ("USP Guideline on Procedures for Mechanical Calibration and Performance Verification Test; Apparatus 1 and Apparatus 2") (1–3). These three dissolution experiments were run for each candidate formulation, and each time, the manufacturing parameters were altered. The selection criteria for moving a candidate forward were two-fold: 1) low intra-experimental variability and 2) a significant difference observed between the perturbed experiment and baseline and non-degassed experiments. Ultimately, a single formulation was selected that satisfied the above experimental conditions for both apparatus 1 and 2.

Characteristics of the final DPVS – Prednisone (lot F161Y0) formulation compared to the previous USP Prednisone Tablets RS are shown in Table 1. The decrease in intra-experimental variability was most significant for experiments with Apparatus 1 (basket). A modest decrease in the variability using Apparatus 2 (paddle) was also observed.

Table 1. Comparison of PVT Acceptance Criteria for Dissolution Systems with Six Positions Using Old and New Prednisone Reference Standard (RS) Tablets

USP Apparatus	Dissolution Test Stage	Prednisone RS (old formulation)		DPVS - Prednisone (lot F161Y0)	
		GM (% Dissolved)	%CV	GM (% Dissolved)	%CV
1 (basket)	Single stage	47–76	16	81–91	4.6
	Stage 1 of 2	51–70	12	83–89	3.4
2 (paddle)	Single stage	27–37	8.3	46–58	6.2
	Stage 1 of 2	28–35	6.2	48–56	4.6

PVT: performance verification test; GM: geometric mean; CV: coefficient of variation.

WHEN DID THE TRANSITION TO THE NEW DPVS – PREDNISONE OCCUR?

The transition to DPVS – Prednisone for use in the PVT requires revision of GC <711> and making the physical reference standard available in the USP product catalog. Stakeholders became aware of the new PVT reference standard when the Initial Notice of Intent to Revise (NITR) GC <711> was posted on Oct 29, 2021, which was updated on Jan 28, 2022. An Interim Revision Announcement (IRA) was posted on Sept 1, 2022, with a public comment period that ended on Jan 31, 2023. The revised GC <711> with DPVS – Prednisone became official on May 1, 2023 (*1*). From this point forward, DPVS – Prednisone is the only reference standard to be used in the PVT to demonstrate apparatus suitability for apparatus 1 and 2.

WHERE TO FIND MORE INFORMATION

The following resources are currently available for readers who would like more information about new USP DPVS – Prednisone tablets:

- General information regarding the PVT procedure: www.usp.org/small-molecules/pvt
- Information about the product: www.usp.org/dissolution

DPVS – Prednisone has been available in the USP catalogue since January 2023. Additional information and answers to frequently asked questions not covered in this report are available in the USP online store: store.usp.org/product/1222818.

QUESTIONS AND ANSWERS

As part of the webinar, commonly asked questions as well

as questions received from the live audience and their answers were presented. A summary of these questions and answers follows.

Note: the answers provided here have been abbreviated for publication and are the opinions and interpretations of the authors. These answers are not necessarily the official viewpoints of the USP.

Frequently Asked Question Related to the Transition to DPVS – Prednisone

Q. Will the old formulation of USP Prednisone Tablets RS be discontinued?

A. Yes, the USP Prednisone Tablets RS were discontinued along with the official revision of GC <711>, which indicates that the new DPVS – Prednisone tablet became official on May 1, 2023 (*1*). Therefore, the USP Prednisone Tablet RS is no longer valid for use in PVT as of this official date (May 1, 2023), even though the PVT tablets had a valid use date of July 31, 2023 on the label. The label is incorrect.

Q. Is a PVT performed before the revision to GC <711> still valid after the revision becomes official on May 1, 2023?

A. Yes, the chapter revision will not require laboratories to recalibrate an instrument qualified using USP Prednisone Tablets RS in the PVT before the official date. After May 1, 2023, the new DPVS – Prednisone tablet must be used to requalify apparatus 1 or 2 according to the updated GC <711> (*1*).

Q. Will there be significant changes to the mechanical and PVT processes with the introduction of DPVS – Prednisone?

A. No. Other than minor changes in the handling and storage conditions for the DPVS – Prednisone tablets, the mechanical calibration procedure prior to conducting the PVT, including standard preparation procedures, remains the same. For example, the new product has a push-through backing on the blister package, so there is no need to peel the backing off.

Q. Will the USP provide guidance documents and resources like the USP Dissolution Toolkit to assist with mechanical and PVT calibration with the new DPVS – Prednisone tablets?

A. Yes, the updated guideline was made available in March 2023 on the USP website (see www.usp.org/pvt), along with numerous video resources specific to DPVS – Prednisone tablets (*3*).

Attendee Questions During the AAPS/USP DVPS Workshop

Q. Has USP demonstrated a correlation between failing commercial batches and failing DPVS results?

A. Not currently; however, it is a research objective that USP intends to pursue. Some may argue that "the USP Prednisone Tablet is quite sensitive; however, my product is not as sensitive." It is important to note here that operational characteristics of a dissolution system that is not passing the PVT may be a result of perturbations within the dissolution apparatus that tend to increase the dissolution results. The reassurance here is that once the apparatus has passed stringent acceptance criteria for a sensitive product, then it should be sufficient to evaluate commercial batches, whether sensitive or not.

Q. What happens if a commercial lot passes dissolution acceptance criteria at initial release, then later fails with a dissolution apparatus that passes PVT acceptance criteria using DPVS – Prednisone?

A. From a USP perspective, if an apparatus passes with the new DPVS, it meets the compliance requirement according to GC <711>. Issues with conformance of the commercial product to acceptance criteria may be more of a compliance question for the U.S. Food and Drug Administration.

Q. Does the new DPVS use the same stage 1 and 2 paradigm? Is it still necessary to decide which approach to use before testing, as with the previous PVT (i.e., do you declare whether you'll use 12 or 6 units for testing)?

A. Yes, the same paradigm is used. This approach was adopted in 2010 when USP changed acceptance criteria to be based on geometric mean and coefficient of variation (CV) (2). Single-stage testing with 12 units (i.e., six units tested back-to-back) gets maximum use from the GM and CV acceptance criteria ranges. In contrast, two-stage testing (with 6 units in stage 1 and 6 more units in stage 2, if required) has tighter initial acceptance criteria in stage 1, and slightly tighter criteria in stage 2, compared with single-stage testing. USP resources are available to explain the statistical reasoning for stage testing by statistician, Walter Hauck, published in 2011 (*4*).

Q. Can we anticipate changes to DPVS formulation stability, such as a change in acceptance criteria, which had happened in previous formulations of the previous Prednisone PVT tablets?

A. Controlled stability studies were performed with accelerated and long-term conditions, demonstrating stability of the dissolution values and sensitivity to perturbations over time. As with all new USP standards, we conduct constant performance monitoring using products stored at the USP facility, and with this DPVS, the performance and test results have been consistent throughout the monitoring period. No changes are anticipated.

Q. Do we push the DPVS tablets through the foil on the blister package, because it was noticed there is no tab to pull back the aluminum on the blister pack?

A. Yes, the tablets are meant to be pushed through the backing of the blister package.

Q. What is the difference between the "USP Guideline on

Procedures for Mechanical Calibration and Performance Verification Test Apparatus 1 and 2" and the older version of the USP Dissolution Toolkit (*2*, *3*)?

A. Mostly subtle changes were made to some of the methods used in the mechanical calibration procedures, and the PVT procedure was updated to include the DPVS – Prednisone product.

Q. Regarding reformulation of the product, because the new product is heavier, does this mean that there is more excipient present or does this simply mean that the tablet has higher density compared to the old formulation?

A. Both factors, more excipients and an increase in tablet hardness, likely contribute to the increased mass of the new formulation.

Q. Is degassing of the dissolution media as critical with the new formulation? If so, is there a recommended method for degassing the dissolution media?

A. The degassing method is still in the "USP Guideline on Procedures for Mechanical Calibration and Performance Verification Test Apparatus 1 and 2" document, and videos describing the USP degassing method are available at the PVT website (www.usp.org/small-molecules/pvt) (*3*). As part of the transition process, collaborative studies were conducted with both the old and new formulations. The test procedure was the same for both products; hence, degassing was required for both. By extension, the new product requires media degassing as part of the experimental setup. Further studies will be conducted by USP to understand the impact of media degassing relative to the impact of other operational and setup parameters for the dissolution apparatus.

Q. Has there been studies of DPVS – Prednisone with either the 2-L vessels or small-volume vessels?

A. USP has conducted studies with reduced volumes, specifically with small-volume vessels that meet the requirements of the *Chinese Pharmacopeia*, but not with large-volume vessels. Further studies will be conducted by USP to investigate the impact of changes in volume on the dissolution of DPVS – Prednisone.

Q. Has any testing of the new DPVS – Prednisone formulation been done in apex vessels?

A. There is an active study to characterize apex vessels. After characterization of the apex vessels, studies will be conducted using the new DPVS – Prednisone formulation. In development of the new formulation, standard 1-L vessels were used for typical apparatus 1 and 2 dissolution testing.

Q. Because DPVS – Prednisone tablets are in the new sachet packaging configuration, what storage conditions are recommended?

A. Like all USP reference standards, the user should store the standard according to the instructions on the label. The old formulation of USP Prednisone Tablets RS required storage in dry conditions (not more than 40% RH at room temperature). The new DPVS – Prednisone formulation requires storage at controlled room temperature.

Q. Can autosampling be used with DPVS – Prednisone instead of manual sampling?

A. When the collaborative studies were conducted, manual sampling was required as part of the test protocol. The specification ranges shown on the product certificate are based on a manual sampling procedure. As with any modification to a procedure, it is incumbent on the end user to validate autosampling against the manual sampling method.

SUMMARY

The aim of this webinar was to provide information to dissolution practitioners regarding changes to *USP* GC <711> related to the introduction of a new reference standard to be used to demonstrate apparatus suitability for apparatus 1 and 2. The new USP DPVS - Prednisone tablets have been reformulated and redesigned to address concerns about variability, sensitivity, and stability. As of May 1, 2023, DPVS – Prednisone is the only reference standard to be used in the PVT for apparatus 1 and 2.

To provide feedback on DPVS - Prednisone, complete the survey at the following link: uspta.qualtrics.com/jfe/form/SV_b2S249T6JSVeemG?Source=DisTechArticleML.

DISCLOSURES

This USP webinar was sponsored by the American Association of Pharmaceutical Scientists and AAPS In Vitro Release and Dissolution Testing Community. Mark Liddell is a paid employee of the USP. The other authors have no conflicts of interest.

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